REMARKS

I. Amendments to the Claims

Claims 23 and 73 have been amended solely to promote the allowance of the case and without acquiescing to the Examiner's rejection. Claim 77 has been added. The claims are supported by the originally filed specification, for example, page 5, lines 12-19, page 8, lines 3-12, page 9, lines 7-9 and page 20, lines 20-24. No new matter has been added.[1]

Claims 23, 29, 73, and 76-77 are pending. Applicant respectfully submits that the pending claims are allowable for the following reasons.

II. Arguments and Response to Rejection

1. Vogelsang *et al.* does not render the claimed invention obvious

In the Office Action, the Office has maintained the rejection of claims 23, 29, 73 and 76 under 35 U.S.C. § 103(a) as being unpatentable over Vogelsang *et al.* (*N. Engl. J. Med.*, 1992, vol. 326, pages 1055-1058, "Vogelsang *et al.*") in view of Kaplan (U.S. Patent No. 5,385,901, "Kaplan"). (Office Action, pages 3-6). The Office alleges that Vogelsang *et al.* discloses the administration of thalidomide to patients with chronic graft-versus-host disease whose primary diagnosis was chronic myelogenous leukemia (Table 1), and thus the reference teaches the administration of thalidomide to patients having blood-born tumors and leukemia. *Id.* Applicant respectfully traverses this rejection.

Applicant reiterates that the instant claims are not *prima facie* obvious over Vogelsang *et al.* in view of Kaplan for the reasons set forth in all of Applicant's Responses of record. Nevertheless, solely to promote the allowance of the case and without acquiescing to the Examiner's rejection, the claims have been amended to exclude "treating leukemia patients who also have graft-versus-host disease." The Office Action states that "the instant claims do not preclude treating leukemia patients who also have graft-versus-host disease." Pages 5-6 of the Office Action. In view of the amendments, the rejection has become moot and should be withdrawn.

Simply put, Vogelsang *et al.* teaches the treatment of a different disease, graft-versus-host disease by a different mechanism of action (TNF-α inhibition). Applicant invented and wishes to claim the treatment of blood-born tumors via an anti-angiogenesis. Thus, Applicant is claiming treatment of different patients, those having blood-born tumors, not

[1] *See* also Column 12, lines 10-12 of U.S. Patent No. 5,629,327

graft-versus-host disease. The claims have been amended to make this distinction clear.[2] Given the above amendments, the rejection is moot.

2. **Kaplan does not cure deficiency of Vogelsang *et al.***

Nevertheless, the Office Action states (1) that Kaplan teaches the oral administration of thalidomide in controlling abnormal concentrations of TNF-α; (2) that it would be obvious to administer thalidomide to chronic myelogenous leukemia patients having chronic graft-versus-host disease via administration routes taught in Kaplan. (pages 4-6 of Office Action). Applicant respectfully traverses this rejection.

Kaplan does not remedy the deficiency of Vogelsang *et al.*, because Kaplan reports on the TNF-α inhibition activity of thalidomide and its use for controlling abnormal concentrations of TNF-α in different diseases, Cachexia, septic shock and HIV infection (Abstract and Column 3). Again, this is not what is currently claimed (treating blood-born tumors). Thus, Kaplan teaches away from the treatment of the recited tumors by focusing on the use of thalidomide for treating the different diseases.

In fact, Kaplan discloses that TNF-α is associated with the destruction of tumor cells as its name suggests (Column 2, lines 60-62). Therefore, when reading the teaching of Kaplan, a skilled artisan would have understood that thalidomide is not effective in treating tumors, because thalidomide inhibits TNF-α production. Accordingly, Kaplan teaches away from what is claimed, or at least there is no motivation to combine the teachings of Vogelsang and Kaplan to treat tumors. The Office has not pointed to any reason that would have prompted a person skilled in the art to combine Vogelsang and Kaplan for treating blood-born tumors as claimed. The law of obviousness requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention. *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1379 (Fed. Cir. 2006). (Emphasis added). In this case, there is no motivation to combine the teachings of Vogelsang and Kaplan in the claimed manner.

Further to support that Kaplan teaches away from the claimed invention and there is no motivation to combine Vogelsang and Kaplan to treat tumors, Applicant respectfully submits herewith Declaration of Dr. Ohno. This Declaration was filed before the Japanese Patent Office during the prosecution of the corresponding Japanese Patent No. 4065373. During the prosecution of the Japanese Patent, Kaplan's corresponding PCT Publication No.

[2] The Examiner is invited to suggest alternative language as the purpose should be clear. The claimed invention is not directed to the treatment of graft-versus-host disease, but to the treatment of blood-born tumor.

WO 92/14455 was cited as Reference F in negating inventiveness of the application for its teaching that thalidomide inhibits TNF-α production (in Office Action issued on October 24, 2006 by Appeal examiner). In response to the rejection, Dr. Ohno opined on the teachings of the cited art including Kaplan. *See* paragraphs 11-13 of Dr. Ohno's Declaration. [3]

In particular, Dr. Ohno stated that, in the early 1990's, TNF-α itself was considered and studied as an anti-cancer agent, and thus it was not obvious to inhibit TNF-α to treat cancers as of the priority date of this application. *See* paragraphs 12-13 of Dr. Ohno's Declaration. He opined that, as of the priority date of the present application, a skilled person would not have considered the inhibition of TNF-α for treating cancers, and thus a skilled person would not have combined and could not have combined the cited references (including Kaplan) to treat cancers. *See* paragraph 13 of Dr. Ohno's Declaration.

In this regard, to support his opinion, Dr. Ohno cited Taguchi *et al.*, (3)2 *Biotherapy* 177-86 (1991), a copy of which is submitted herewith. [4] Applicant submits further publications to support Dr. Ohno's opinion. Creagan ET *et al.*, *Cancer*, 1988, 62: 2467-2471), Beutler B, *Hospital Practice*, 1990, 25: 45-56, citing that numerous articles referred to therein clearly show such recognition in the relevant art regarding anticancer activity of TNF as of the priority date. [5]

Further, even if Vogelsang were combined with Kaplan as the PTO alleges, a skilled person would have no reason to use thalidomide for treating tumors, because the combined teachings do not provide the legally required reasonable expectation of success. When the references are combined, one skilled in the art is merely taught that thalidomide may be used for treating chronic graft-versus-host disease, Cachexia, septic shock and HIV infection as disclosed in Vogelsang or Kaplan, but not for treating any tumors, because the references do not teach that thalidomide was effective in treating tumors, much less blood-born tumors. As such, Vogelsang in view of Kaplan does not provide any reasonable expectation that

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[3] Before the Japanese Patent Office, inventiveness of the Japanese counterpart was recognized based on Dr. Ohno's Declaration and Taguchi *et al.* in support thereof, which was resulted in the issuance of the Japanese patent.

[4] Applicant requests that the references submitted be made of record in the file history of the application and that the Examiner execute the 1449 Form enclosed. *See* page 177 of Taguchi, left column, Introduction, lines 11 to 25 suggesting to consider TNF as a promising agent for cancer therapy.

[5] Applicant requests that the references submitted be made of record in the file history of the application and that the Examiner execute the 1449 Form enclosed. *See* page 2467, left column, lines 4 to 7 and left column, line 17 to right column, line 9 of Creagan ET *et al.* *Also see* page 45, left column, lines 31 to 32, page 51, right column, lines 18 to 20, and page 56, right column, lines 4 to 8 of Beutler B.

thalidomide could be successfully used in treating blood-born tumors. (*Medichem, S.A. v. Robaldo,* 437 F.3d 1157, 1165 (Fed. Cir. 2006); *O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988)).

Applicant respectfully submits that the instant claims are not obvious over the cited references, and requests that this rejection be withdrawn.

3. Unexpected results support the nonobviousness of the instant claims

Even assuming, *arguendo*, a *prima facie* case of obviousness were established, there is evidence of unexpected results for the claimed invention that rebuts any such *prima facie* case. As is well settled, even if a *prima facie* case of obviousness is established, the Examiner is required to consider all rebuttal evidence submitted by an applicant. *See In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-Mcneil Pharmaceutical v. Mylan Laboratories*, 348 F.Supp.2d 713, 755 (N.D.W.Va. 2004); and *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). *See also* MPEP §2145. As the Court explained, "[w]hen a patent applicant puts forth rebuttal evidence, the Board must consider that evidence." *In re Sullivan*, at 1351. Such rebuttal evidence includes "evidence of unexpected results." *Id.*, citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007).

Indeed, in a divisional application no. 11/096,155, the Office has acknowledged that "it is surprising and unexpected that thalidomide has now been found to be effective in the treatment of blood-born tumors." (page 2 of Notice of Allowability dated January 12, 2010). The Office stated that the post filed art demonstrates that thalidomide is effective to treat blood-born tumors, referring to references C317-C333 cited in the divisional application. *Id.*

C317-C333, mentioned in Notice of Allowability of the divisional application, were also submitted in this application, to support that thalidomide is effective in treating blood-born tumors[6]. *See* C318-C334 filed on March 14, 2008.

For example, for effective of thalidomide in treating leukemia, Applicant submitted Furman *et al.*(*Abstract #6640*, 2005 and *Abstract* #4835, 2004) reporting on the study of thalidomide in treating patients with chronic lymphocytic leukemia (CLL); Steins *et al.* (*Blood*, 2002; *Leukemia & Lymphoma,* 2003; and *European Journal of Hematology*, 2007) describing that thalidomide is effective in treating patients with acute myeloid leukemia

[6] The articles were submitted to the Office on April 19, 2007, July 12, 2007, October 31, 2007, March 14, 2008 and Feb. 25, 2009, together with supplemental IDS and list of references cited (*e.g., see* C318-C334 and C347-373 references). All of these references were made of record in the file history of the application.

(AML); Strupp *et al.* (*Leukemia Research,* 2005) reporting on study of patients with hairy cell leukemia (HCL); and Wohrer *et al.* (*The Hematology Journal,* 2004) reporting on effective treatment of plasma cell leukemia.

For effectiveness of thalidomide in treating lymphoma, Applicant submitted Ruan *et al.* (*Abstract* #2751, 2006), Damaj (*Leukemia*, 2003) and Goy (*Clinical Lymphoma & Myeloma,* 2006) which describe that thalidomide is effective in treating mantle cell lymphoma (MCL); Game *et al.* (*Abstract* #5235, 2001) report on treating non-Hodgkin's lymphoma (NHL); Larson *et al.* (*Clinical Advances in Hematology & Oncology*, 2005) report on HIV-related lymphoma; and Ramasamy *et al.* (*Haematologica*, 2006) report on angioimmunoblastic T-cell lymphoma.

Further, Folkman (*Nature Review*, 2007) was submitted, discussing thalidomide studies in treating multiple myeloma and various tumors such as NHL, AML, CLL and leukemias (page 276). *See also* for beneficial actions in treating multiple myeloma, *e.g.,* Kneller A. *et al.* (Therapy with thalidomide in refractory multiple myeloma patients - the revival of an old drug. *British Journal of Haematology* 2000; 108(2): 391-3); Hideshima T. *et al.* (Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood* 2000; 96(9): 2943-50); Barlogie B. *et al.* (Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. *Blood* 2001; 98(2): 492-4); Diggle (*IJCP*, November 2001, Vol. 55, No. 9, pp. 627-631; Singhal, *et al.* (*Biomed. Pharmacother.* 2002; 56:4-12); and Rajkumar (*Mayo Clin Proc.* July 2004; 79(7):899-903).

In sum, the publications as a whole support unexpected results of the claimed invention using thalidomide in treating blood-born tumors. Applicant, therefore, respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

III. Conclusion

Applicant respectfully requests that the above amendment and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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